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(54) New pharmaceutical compositions comprising esters or amides as active ingredients.

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CH-A- 634 749
DE-A- 2 819 447
DE-A- 3 042 975
DE-A- 3 411 910
GB-A- 1 544 576
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CHEMICAL ABSTRACTS, vol. 101, 1984, page 318, abstract no. 43519x, Columbus, Ohio, US; M. DJIMBO et al.: "Release of drugs formulated as hard pastes filled into hard gelatin capsules. Part 1. physical properties and in vitro testing."

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Description

The present invention is concerned with new pharmaceutical compositions comprising esters or amides as active ingredients. More particularly, it relates to pharmaceutical compositions characterized in that esters or amides are suspended or dissolved in middle chain glycerides (referred to as "MCG" hereafter) or mixtures thereof. The degradation of the esters or amides by digestive enzymes (e.g. esterases and peptidases) is inhibited by suspending or dissolving the said esters or amides in MCGs.

Out of many esters, various esters of guanidinobenzoic acid are known to be useful as medicines, for example, useful in the treatment of acute pancreatitis owing to their anti-plasmin activity and anti-trypsin acitivity and in the treatment of pulmonary emphysema owing to their inhibitory activity on elastase.

Recently, as a result of their detailed research on pharmacokinetics in oral administration of the above esters, the present inventors have found unexpected facts. That is, it has been confirmed that these esters are degraded by the action of various esterases in the digestive system, especially in the intestine comparatively rapidly.

Esters of guanidinobenzoic acid are degraded to guanidino benzoic acid and an alcohol corresponding to the ester moiety (when a medicine has plural ester-bonds, it is presumed that the bonds are severed in order of facility in breaking and finally the medicine is degraded to guanidinobenzoic acid and another part. Any degradation products have no desired pharmacological effect or have the structure not to be absorbed, and therefore, the bioavailability of the esters of guanidinobenzoic acid descends.

Furthermore, it has turned out that other esters and amides which are considered to be degraded by the action of various esterases and peptidases in digestive system, are degraded comparatively rapidly, similarly to esters of guanidinobenzoic acid.

As a result of their energetic investigation in order to find means to inhibit the degradation of the esters or amides by the action of digestive enzymes (e.g. various esterases and peptidases) in digestive system, the present inventors have found that the purpose is accomplished by suspending or dissolving the said esters or amides in MCGs, and have completed the present invention.

In the specification of the Japanese Patent Kokai No. 55-17328, W/O/W-formed emulsion comprising insulin as active agent and middle chain triglycerides (referred to as "MCT" hereafter) as oily substance, and inhibiting the degradation by the action of digestive enzymes, is disclosed. In the composition, MCT is used as oily substance which the oily phase in W/O/W-formed emulsion is composed of. There is a fundamental difference in structure from the MCG suspensions or solutions of the present invention, and further, such W/O/W-formed emulsion does not suggest the present invention at all.

Furthermore, no other prior art relating to MCGs suspensions or solutions for inhibiting the degradation of active ingredients by the action of digestive enzymes, is known. Further, no compositions comprising suspensions or solutions of guanidinobenzoic acid derivatives in MCGs have so far been known.

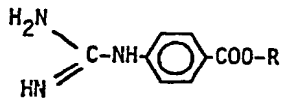
Figure 1 to 8 are the time-course of the remaining ratio of the active ingredient in the parmaceutical composition of the present invention, in small intestine, and Fig. 1, 2, 3, 4, 5, 6, 7 and 8 relate to Compound A, Compound B, Compound C, Compound D, Compound E, Compound F, Compound G and Compound H, respectively.

Accordingly, the present invention is concerned with parmaceutical compositions which essentially consists of an ester of benzoic acid or thromboxane analogues, an amide of benzoic acid, thromboxanes analogues or prostaglandin analogues, or prolinal or thiazolidine derivatives having amido bond(s) suspended or dissolved in middle chain glycerides (referred to as "MCG" hereafter) or a mixture of two or more of them.

Compositions comprising glycosides, antibiotics having ester bonds and nifedipine, with MCGs are disclosed in the specifications of the British Patent Publication No. 1544576, the European Patent Publication No. 108295 and the Japanese Patent Kokai Nos 58-170788 and 59-106418.

The CH-A-634 749 discloses a composition comprising valethamat-bromide and MCGs.

Of the esters of benzoic acid, compounds being an ester of p-guanidinobenzoic acid as fundamental chemical structure are preferred. Especially preferably, the esters are compounds of the general formula :



(I)

(wherein R is an organic group) and non-toxic acid-addition salts thereof. They are described in detail, for example, in the specification of the Japanese Patent Kokai Nos. 50-4038, 51-16631, 51-54530, 51-75042, 52-

89640, 53-147044, 54-70241, 55-55154, 55-100356, 55-115863, 55-115865, 56-34662 and 57-53454, and of the British Patent Nos. 1472700, 2007653, 2044760 and 2057435, and of the European Patent Publication No. 222608. Compounds wherein R is a substitued aromatic group in the general formula (I) are more preferred. Such compounds are p-(p-guanidinobenzoyloxy)phenylacetic acid N,N-dimethylcarbamoylmethyl ester, p-guanidinobenzoic acid p-sulfamoylphenyl ester, p-guanidinobenzoic acid 6-amidinonaphth-2-yl ester and non-toxic acid-addition salts thereof. p-Guanidinobenzoic acid methyl ester and non-toxic acid-addition salts thereof are also preferred.

Other preferable esters of benzoic acid are esters of salicylic acid, eg salicylic acid ethyl ester.

The esters of thromboxane analogues used in the present invention are the compounds described in the specification of the British Patent Publication No. 2184118 and of the European Patent Publication Nos. 44771 and 171146. Such compounds are, for example, alkyl esters of 7-(3-tosylaminobicyclo [2.2.1]heptan-2-yl)-5Z-heptenoic acid.

Compositions comprising cyclosporins and antibiotics having amido bonds, with MCGs are disclosed in the specification of the British Patent Publication No. 2015339 and of the European Patent Publication No. 108295 and of the Japanese Patent Kokai No. 58-170788. GB-A- 1544576 discloses a composition comprising the amide chloramphenical and medium chain fatty acid triglycerides.

Of the amides of prostaglandin analogues used in the invention the preferred compounds are disclosed in the specifications of the European Patent Publication Nos. 156611, 182231 and 232126, and of the French Patent Publication No. 2376134 and further in the Chemical Abstracts, abstract Nos. 77743g (1976), 43438a (1976) and 131213h (1975). Such compounds are, for example, amides of 6-keto-16S, 18S-ethano-20-ethyl-PGE_1 with an amino acid.

Of the amides of benzoic acid used in the invention the preferred compounds are disclosed in the specification of the European Patent Publication No. 173516.

Of the amides of thromboxane analogues used in the invention the preferred compounds are disclosed in the specification of EP-A-0312906. Such compounds are, for example, amides of 7-(3-tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptenoic acid with an amino acid.

Of the prolinal or thiazolidine derivatives having amido bonds used in the invention the preferred compounds are disclosed in the specification of EP-A- 0268190 and of the Japanese Patent Kokai No. 64-6263. Such compounds are, for example, N-[3-[N-4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal.

Pharmacological effects of esters or amides used in the compositions of the present invention are not limited. For example, the esters of p-guanidinobenzoic acid of the general formula (I) have inhibitory effects on proteinases such as anti-plasmin activity, antitrypsin activity, and therefore may be useful in the treatment of acute pancreatitis, or they have an inhibitory effect on elastase, and therefore may be useful in the treatment of pulmonary emphysema.

MCGs in the present invention mean a monoglyceride of a fatty acid of 4 to 10 carbon atoms (referred to as "MCM" hereafter), a corresponding diglyceride (referred to as "MCD" hereafter) and a corresponding triglyceride (referred to as "MCT" hereafter), and a mixture of two or more of them. The fatty acids having any carbon atoms are preferred. Glycerides of caprylic acid and of capric acid are more preferred. Glyceryl monocaprylate, glyceryl dicaprylate and glyceryl tricaprylate, and a mixture thereof are especially preferred. MCGs used in the present invention are on the market with trade marks, e.g. Migryol and Imwitor (both prepared by Dynamite Novel Co.) and Panacete (prepared by Nippon Yushi Co.).

The use of MCGs to improve the bioabsorbability of antibiotics (GB-A- 2 015 339) and the amide chloramphenical (GB-A- 1 544 576) or to improve the stability of unstable drugs (DE-A- 2 819 447) is known in the art. DE-A- 3 042 975 discloses a composition comprising aspirin and an amphiphilic substance like lecithine.

The suspension composition or solution composition of the present invention may, if desired, comprise other inert additional substances, for example, viscosity-lowing agents such as phospholipids and non-ionic surface-active agents, and specific gravity-controlling agents such as calcium carbonate, calcium citrate and calcium gluconate.

The pharmaceutical compositions of the present invention may be prepared by adding esters or amides, and, if desired, other additional substances into MCGs, and suspending or dissolving the mixture by known methods.

The obtained suspensions or solutions may be administered as they are (directly), and preferably administered in the form of capsules formulations filled into gelatin-made soft capsules or gelatin-made hard capsules. If necessary, the said capsule formulation may be coated with an enteric coating. Any enteric coatings being unreactive with active ingredients may be used. Preferable examples of enteric coatings used are carboxymethylethyl cellulose, hydroxypropylmethyl cellulose acetate succinate and phospholipids. The preparation of capsules and the coating with enteric coating may be carried out by known methods.

[Effects]

The pharmaceutical compositions of the present invention may inhibit the degradation of esters or amides by the action of digestive enzymes in digestive system, and therefore the bioavailability of the active ingredient remarkably ascends.

[Examples]

The following examples, reference examples and experiments illustrate, the present invention in detail.

Example 1

A mixture of 250 g of p-(p-guanidinobenzoyloxy)phenylacetic acid N,N-dimethylcarbamoylmethyl ester methanesulfonate, 740 g of glyceryl tricaprylate (Panacete® 800, prepared by Nippon Yushi Co.) and 10 g of bean lecithin (prepared by Hohnen Seiyu Co.) was stirred enough and then sieved through a 100-mesh sieve to obtain the desired suspension of the present invention.

Example 2

By the same procedure as described in Example 1, the suspension of the present invention was obtained by using 250 g of p-guanidinobenzoic acid 6-amidinonaphth-2-yl ester dimethanesulfonate, 740 g of glyceryl tricaprylate and 10 g of bean lecithin.

Example 3

By the same procedure as described in Example 1, the suspension of the present invention was obtained by using 50 g of p-guanidinobenzoic acid p-sulfamoylphenyl ester methanesulfonate, 940 g of glyceryl monocaprate (Panacete® 1000, prepared by Nippon Yushi Co.) and 10 g of bean lecithin.

Example 4

By the same procedure as described in Example 1, the suspension of the present invention was obtained by using 50 g of p-guanidinobenzoic acid methyl ester methanesulfonate, 940 g of glyceryl monocaprylate (Imwitor® 742, prepared by Dynamite Novel Co.) and 10 g of bean lecithin.

Example 5

By the same procedure as described in Example 1, the suspension of the present invention was obtained by using 250 g of p-(p-guanidinobenzoyloxy)phenylacetic acid N,N-dimethylcarbamoylmethyl ester methanesulfonate, 740 g of a mixture of glyceryl monocaprylate and glyceryl dicaprylate (6 : 4) (Imwitor® 908, prepared by Dynamite Novel Co.) and 10 g of bean lecithin.

Example 6

980 g of glyceryl tricaprylate were added little by little to 20 g of 7-[(1R, 2S, 3S, 4S)-3-tosylaminobicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid ethyl ester and the mixture was stirred enough to obtain the desired solution of the present invention.

Example 7

50 ml of ethanol was added to 250 g of salicylic acid ethyl ester with stirring to give semi-solid solution. To the mixture was added 750 g of glyceryl tricaprylate and the obtained mixture was stirred enough. Ethanol was removed completely from the mixture under vacuum more than an overnight to obtain the suspension of the present invention.

Example 8

10 ml of ethanol was added to 20 g of an amide of 6-keto-16S, 18S-ethano-20-ethyl-PGE_1 with L-leucine.

To the obtained solution was added 980 g of glyceryl tricaprylate and the mixture was stirred enough. Ethanol was removed completely from the mixture under vacuum more than an overnight to obtain the solution of the present invention.

Example 9

A mixture of 50 g of an amide of 7-[(1R, 2S, 3S, 4S)-3-tosylaminobicyclo[2.2.1]heptan-2-yl]-5Z-heptenoic acid with glycine, 940 g of glyceryl monocaprylate and 10 g of polyoxyethylenehydrogenated caster oil (HCO-60®, prepared by Nikko chemicals Co.) was stirred enough to obtain the suspension of the present invention.

Example 10

By the same procedure as described in Example 1, the suspensionn of the present invention was obtained by using 250 g of N-[3-[N-(4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal, 740 g of glyceryl tricaprylate and 10 g of bean lecithin.

Reference Example 1

1000 g of the suspension prepared in Example 1 were filled into water-soluble soft capsules with a rotary-capsule machine by methods known per se to obtain about 2500 capsules.

Reference Example 2

The soft capsules prepared in Reference Example 1 were coated with an aqueous solution containing 12% (w/v) carboxymethylethyl cellulose (CMEC· AQ®, prepared by Freund Sangyo Co.), 3% (w/v) glyceryl caprylate and 1% (w/v) sodium citrate by pan-coating method to obtain enteric-coated soft capsules.

Reference Example 3

The soft capsules prepared in Reference Example 1 were coated with an aqueous solution containing 10% (w/v) hydroxypropylmethyl cellulose acetate succinate (HPMCAS®, prepared by Shin-etsu Kagaku Co.), 2% (w/v) triethyl citrate, 5% (w/v) talc and 0.05% (w/v) hydroxypropylcellulose (HPC-MF®, prepared by Shin-etsu Kagaku Co.) by pan-coating method to obtain enteric-coated soft capsules.

Reference Example 4

1000 g of each suspension or solution prepared in Example 2 to 10 were filled into water-soluble soft capsules with a rotary-capsule machine by methods known per se to obtain 2500 each capsules (100 mg of the active ingredient were contained in each capsules obtained from the composition of Example 2, 5, 7 and 10, and 20 mg of the active ingredient were contained in each capsules obtained from the composition of Example 3, 4 and 9, and further 8 mg of the active ingredient were contained in each capsules obtained from the composition of Example 6 and 8).

Reference Example 5

By the same procedure as described in Reference Example 2, enteric-coated soft capsules were obtained by using soft capsules prepared in Reference Example 4.

Reference Example 6

By the same procedures as described in Reference Example 3, enteric-coated soft capsules were obtained by using soft capsules prepared in Reference Example 4.

Reference Example 7

1000 g of the suspension or solution prepared in Example 1 to 10 were filled into water-soluble hard capsules with an oil and paste filling machine by methods known per se to obtain about 2500 each capsules.

Reference Example 8

By the same procedures as described in Reference Example 2 or 3, enteric-coated hard capsules were obtained by using hard capsules prepared in Reference Example 7.

Experiment 1

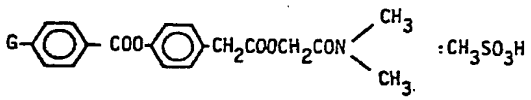
The inhibitory effect of MCG on the degradation of esters of quanidinobenzoic acid in small intestine

The experiment was carried out according to the Yasuhara's method using intestinal loop in rats [see Journal of Pharmacobio-Dynamics, 2, 251 (1979)]. That is, male Sprague-Dawley rats weighing 220-260 g were fasted an overnight prior to surgery ; however drinking water was readily accessible. The rats were anesthetized by sodium pentobarbital using an intraperitoneal injection of 50 mg/kg. The small intestine was exposed by a midline abdominal incision. The intestinal loop studied was used approximately 15 cm of the duodenal-jejunal site that was approximately 2 cm off the outlet of bile duct.

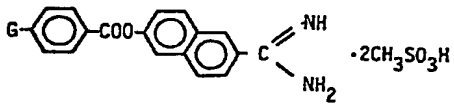
The suspension or solution containing active ingredients was directly administered into the loop and the both ends of the loop were closed. The experiment with Compound F and H was carried out further by adding pancreatic juice and bile of other rats into the loop by cannula. After a given period of time, the loop was cut out. The contents were washed out with physiological salt solution and/or ethanol, and thereto was added a mixture of 0.1N aqueous methanesulfonic acid, 1,2-dichloroethane and isopropanol. The obtained mixture was centrifuged and the resulting supernatant was used as a sample. In the case of Compound D to G, the washings were directly used as a sample. The active ingredient and the degradation products in sample were determined with high pressure liquid chromatography.

Various esters and amides used in the experiments and administration methods thereof

Compound A: p-(p-guanidinobenzoyloxy)phenylacetic acid N,N-dimethylcarbamoylmethyl ester methanesulfonate

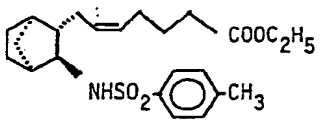


Compound B: p-guanidinobenzoic acid 6-amidinonaphth-2-yl ester dimethanesulfonate

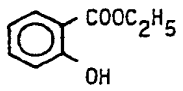


Compound C: p-guanidinobenzoic acid methyl ester methanesulfonate

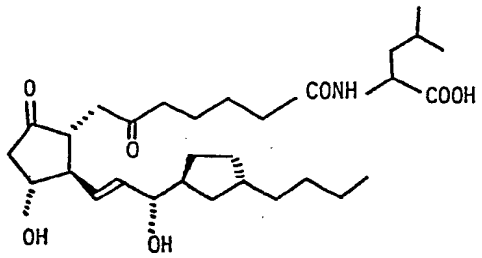
Compound D : 7-(3-tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptenoic acid ethyl ester



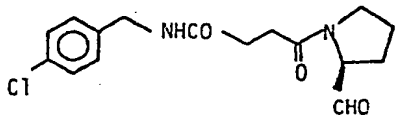
Compound E : salicylic acid ethyl ester



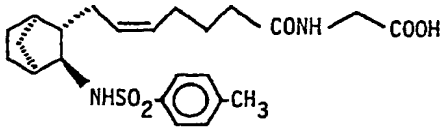
Compound F : 6-keto-16S,18S-ethano-20-ethyl-PGE$_1$ leucine amide



Compound G : N-[3-[N-(4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal



Compound H : 7-(3-tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptenoic acid glycine amide



(wherein G is a guanidino group.)

Administration method

H_2O : dissolving in the ratio of 5 mg of active ingredient/0.5 ml of water/animal.

MCM8(glyceryl monocaprylate) :

suspending in the ratio of 5 mg of active ingredient/0.5 ml of MCM8/animal.

MCT8(glyceryl tricaprylate) :

suspending in the ratio of 5 mg of active ingredient/0.5 ml of MCT8/animal.
The result was shown in Table 1, and Fig. 1 to 8.

Notes

1. 0.5 mg of Compound C were used instead of 5 mg of it and the suspension of Compound C even in water was administered because of its poor solubility.
2. 0.5 ml of physiological salt solution (referred to "SALT") for Compound D instead of water, because of its water-insoluble character.
3. 0.1 mg of Compound F were used because of its strong pharmacological effect, and isotonic phosphate buffer solution (referred to "PHOS") (pH 6.5) instead of water was used because of its water-insoluble character.
4. Compound D, E, F, G and H were previously dissolved in 25 µl of ethanol, and then each compositions of H_2O, MCM8 and MCT8, for administration were prepared.

Table 1

Compound	Administration route	Remaining ratio of the active ingredient in small intestine (% of dose, mean ± S.D)	
		5	15 (minutes after)
Compound A	H_2O (COMPARISON)	58.7± 9.6	12.7± 3.1
	MCM8 (INVENTION)	85.3±21.8	39.7±17.2
	MCT8 (INVENTION)	82.1±18.5	35.5±10.8
Compound B	H_2O (COMPARISON)	68.8± 1.7	27.5± 5.2
	MCM8 (INVENTION)	90.0±15.6	70.5±12.1
	MCT8 (INVENTION)	80.0± 3.2	60.8± 7.5
Compound C	H_2O (COMPARISON)	95.2± 3.1	85.5± 2.5
	MCM8 (INVENTION)	99.1± 3.2	95.5± 1.5
	MCT8 (INVENTION)	97.5± 2.7	92.2± 3.4
Compound D	SALT (COMPARISON)	17.5± 2.9	7.5± 3.4
	MCM8 (INVENTION)	61.3± 9.8	52.7±21.0
	MCT8 (INVENTION)	69.8±12.6	52.1±13.1
Compound E	H_2O (COMPARISON)	49.9±13.7	27.3±16.4
	MCT8 (INVENTION)	70.2±21.0	43.5±15.4
Compound F	PHOS (COMPARISON)	21.5± 8.2	9.2± 4.4
	MCM8 (INVENTION)	37.2± 5.1	35.0±11.3
	MCT8 (INVENTION)	38.4±12.9	35.2± 9.8
Compound G	H_2O (COMPARISON)	62.1± 8.3	26.3±10.4
	MCT8 (INVENTION)	74.5±12.4	40.0±13.1
Compound H	H_2O (COMPARISON)	30.4± 8.1	11.5± 8.5
	MCT8 (INVENTION)	60.8±12.5	50.7±11.9

From the result of Experiment 1, it is understood that the degradation of active ingredients is inhibited by administering the suspension or solution of esters or amides in MCG, compared with by administering the aqueous solution thereof.

Experiment 2

Effect of MCG on bioavailability (1)

When Experiment 1 was carried out by using Compound A and D, blood was collected after a given period

of time (0, 15, 30, 60 and 120 minutes after). The concentration of the active ingredient in blood was determined with high pressure liquid chromatography, and Area Under the plasma concentration-time Curve (AUC) was calculated and then bioavailability (BA) was calculated according to the following formula by comparing with AUC in intravenous administration.

$$BA(\%) = \frac{[AUCid]}{[AUCiv]} \times \frac{[Div]}{[Did]} \times 100$$

[AUCid] : AUC in intraduodenal administration
[AUCiv] : AUC in intravenous administration
[Did] : Dose in intraduodenal administration
[Div] : Dose in intravenous administration

Table 2

	Route	Dose (mg/animal)	AUC (μg·min/ml)	BA (%)
Compound A - Saline[1)]	iv	0.5	602.9± 15.4	100
Compound A - H_2O (COMPARISON)	id	5	182.6± 55.7	3.0
Compound A - MCM8 (INVENTION)	id	5	289.2± 72.6	4.8
Compound A - MCT8 (INVENTION)	id	5	332.1±169.3	5.5
Compound D - Saline[2)]	iv	0.5	327.2± 79.1	100
Compound D - Saline[2)] (COMPARISON)	id	5	25.4± 17.2	0.8
Compound D - MCT8 (INVENTION)	id	5	254.8±102.3	7.8

1) Compound A was dissolved in physiological salt solution for intravenous administration.

2) Ethanol solution of Compound D was diluted with physiological salt solution.

From the result, it is understood that BA in administration of the suspension or solution of esters in MCG is about 1.6 to 9.8 times as superior as BA in administration of aqueous solution of them. The improvement is

of great significance.

Experiment 3

Effect of MCG on bioavailability (2)

Each one soft capsule prepared in Reference Example 1, 2, 3, 4, 5 and 6 (used only a suspension of Example 2 (compound B) in Reference Example 4, 5 and 6) was administered orally with 50 ml of water to six male Beagle dogs fasted an overnight (aged one to two and weighing 10 ± 1 kg). By the same procedures as described in Experiment 2, the concentration of the active ingredient in blood, AUC, and then BA were calculated. The results was shown in Table 3.

Table 3

	Formulation	BA (%)
Compound A	Reference Example 1	10.9± 4.3
	Reference Example 2	18.4± 7.3
	Reference Example 3	17.2±11.5
	Comparison A[1)]	6.3± 2.4
Compound B	Reference Example 4	3.2±1.7
	Reference Example 5	5.0±2.5
	Reference Example 6	5.1±2.1
	Comparison B[1)]	1.7±1.2

1) Comparison : Compound A or Compound B (10 mg/5 ml of water/kg animal body weight) was orally administered.

From the Table 3, it is understood that BA of the composition in which the active ingredient is suspended in MCG is about 1.5 to 3 times as superior as BA of the composition in which it is not suspended in MCG, even in oral administration.

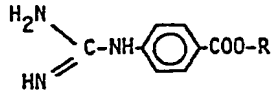
Claims

Claims for the Contracting States AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. A pharmaceutical composition consisting essentially of a compound selected from an ester of benzoic acid or thromboxane analogues, an amide of benzoic acid, thromboxane analogues or prostaglandin analogues, and prolinal or thiazolidine derivatives having amido bond(s) suspended or dissolved in a middle chain glyceride or a mixture of two or more of them.

2. A pharmaceutical composition according to claim 1, wherein said ester is an ester of benzoic acid.

3. A pharmaceutical composition according to claim 2, wherein said ester of benzoic acid is a compound of the general formula :



(I)

(wherein R is an organic group) or a non-toxic acid-addition salt thereof.

4. A pharmaceutical composition according to claim 3, wherein R is a substituted-aromatic group in the general formula (I).

5. A pharmaceutical composition according to claim 4, wherein an ester of guanidinobenzoic acid is :
p-(p-guanidinobenzoyloxy)phenylacetic acid N,N-dimethylcarbamoylmethyl ester,
p-guanidinobenzoic acid p-sulfamoylphenyl ester or
p-guanidinobenzoic acid 6-amidinonaphth-2-yl ester, or
a non-toxic acid-addition salt thereof.

6. A pharmaceutical composition according to claim 3, wherein said ester of benzoic acid is p-guanidinobenzoic acid methyl ester or a non-toxic acid-addition salt thereof.

7. A pharmaceutical composition according to claim 2, wherein said ester of benzoic acid is aspirin or salicylic acid ethyl ester.

8. A pharmaceutical composition according to claim 1, wherein said ester is an ester of thromboxane analogues.

9. A pharmaceutical composition according to claim 8, wherein said ester of thromboxane analogues is an alkyl ester of 7-(3-tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptenoic acid.

10. A pharmaceutical composition according to claim 1, wherein said amide is an amide of prostaglandin analogues.

11. A pharmaceutical composition according to claim 10, wherein said amide of prostaglandin analogues is an amide of 6-keto-16S, 18S-ethano-20-ethyl-PGE_1 with an amino acid.

12. A pharmaceutical composition according to claim 1, wherein said amide is an amide of benzoic acid.

13. A pharmaceutical composition according to claim 1, wherein said amide is an amide of thromboxane analogues.

14. A pharmaceutical composition according to claim 13, wherein said amide of thromboxane analogues is an amide of 7-(3-tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptenoic acid with an amino acid.

15. A pharmaceutical composition according to claim 1, wherein said amide is a prolinal or thiazolidine derivative having amido bonds.

16. A pharmaceutical composition according to claim 15, wherein said prolinal or thiazolidine derivative having amido bonds is N-[3-[N-(4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal.

17. A pharmaceutical composition according to claim 1, wherein said middle chain glyceride is a glyceride of caprylic acid or a glyceride of capric acid.

18. A pharmaceutical composition according to claim 17, wherein said middle chain glyceride is glyceryl monocaprylate, glyceryl dicaprylate or glyceryl tricaprylate, or a mixture thereof.

19. A pharmaceutical composition according to claim 1, which is filled into a capsule.

20. A pharmaceutical composition according to claim 19, characterized in that the capsule is coated with an enteric coating.

21. A pharmaceutical composition according to claim 20, characterized in that the enteric crating is carboxymethylethyl cellulose, hydroxypropylmethyl cellulose acetate succinate or phospholipids.

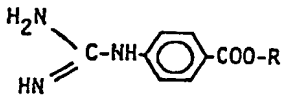
22. A process for the preparation of a pharmaceutical composition wherein a compound selected from an ester of benzoic acid, or thromboxane analogues, an amide of benzoic acid, thromboxane analogues or prostaglandin analogues, and prolinal or thiazolidine derivatives having amido bond(s) is suspended or dissolved in a middle chain glyceride or a mixture of two or more of them.

Claims for the Contracting States ES, GR.

1. A process for the preparation of a pharmaceutical composition wherein a compound selected from an ester of benzoic acid, or thromboxane analogues, an amide of benzoic acid, thromboxane analogues or prostaglandin analogues, and prolinal or thiazolidine derivates having amido bond(s) is suspended or dissolved in a middle chain glyceride or a mixture of two or more of them.

2. A process according to claim 1, wherein said ester is an ester of benzoic acid.

3. A process according to claim 2, wherein said ester of benzoic acid is a compound of the general formula:



(I)

(wherein R is an organic group) or a non-toxic acid-addition salt thereof.

4. A process according to claim 3, wherein R is a substituted-aromatic group in the general formula (I).

5. A process according to claim 4, wherein said ester of guanidinobenzoic acid is :
p-(p-guanidinobenzoyloxy)phenylacetic acid N,N-dimethylcarbamoylmethyl ester,
p-guanidinobenzoic acid p-sulfamoylphenyl ester or
p-guanidinobenzoic acid 6-amidinonaphth-2-yl ester, or
a non-toxic acid-addition salt thereof.

6. A process according to claim 3, wherein said ester of benzoic acid is p-guanidinobenzoic acid methyl ester or a non-toxic acid-addition salt thereof.

7. A Process according to claim 2, wherein said ester of benzoic acid is salicylic acid ethyl ester.

8. A process according to claim 1, wherein said ester is an ester of thromboxane analogues.

9. A process according to claim 8, wherein said ester of thromboxane analogues is an alkyl ester of 7-(3-tosyliminobicyclo[2.2.1]heptan-2-yl)-5Z-heptenoic acid.

10. A process according to claim 1, wherein said amide is an amide of prostaglandin analogues.

11. A process accoding to claim 10, wherein said amide of prostaglandin analogues is an amide of 6-keto-16S, 18S-ethano-20-ethyl-PGE_1 with an amino acid.

12. A process according to claim 1, wherein said amide is an amide of benzoic acid.

13. A process according to claim 1, wherein said amide is an amide of thromboxane analogues.

14. A process according to claim 13, wherein said amide of thromboxane analogues is an amide of 7-(3-tosylamino-bicyclo [2.2.1]heptan-2-yl)-5Z-heptonic acid with an amino acid.

15. A process according to claim 1, wherein said amide is a prolinal or thiazolidine derivative having amido bonds.

16. A process according to claim 15, wherein said prolinal or thiazolidine derivative having amido bonds is N-[3-[N-(4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal.

17. A process according to claim 1, wherein said middle chain glyceride is a glyceride of caprylic acid or a glyceride of capric acid.

18. A process according to claim 17, wherein said middle chain glyceride is glyceryl monocaprylate, glyceryl dicaprylate or glyceryl tricaprylate, or a mixture thereof.

19. A process according to claim 1, wherein said pharmaceutical composition is filled into a capsule.

20. A process according to claim 19, characterized in that the capsule is coated with an enteric coating.

21. A process according to claim 20, charaterized in that the enteric coating is carboxymethylethyl cellulose, hydroxypropylmethyl cellulose acetate succinate or phospholipids.

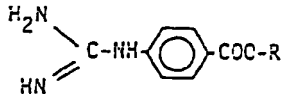
Ansprüche

Patentansprüche für die Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. Arzneimittel, bestehend im wesentlichen aus einer in einem mittelkettigen Glycerid oder einer Mischung aus zwei oder mehreren derselben suspendierten oder gelösten Verbindung, ausgewählt aus einem Ester der Benzoesäure oder von Thromboxananalogen, einem Amid der Benzoesäure, von Thromboxananalogen oder von Prostaglandinanalogen und Prolinal- oder Thiazolidinderivaten mit Aminobindung(en).

2. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß der Ester aus einem Ester der Benzoesäure besteht.

3. Arzneimittel nach Anspruch 2, dadurch gekennzeichnet, daß der Ester der Benzoesäure aus einer Verbindung der allgemeinen Formel :



(I)

worin R für eine organische Gruppe steht, oder einem nichttoxischen Säureadditionssalz derselben besteht.

4. Arzneimittel nach Anspruch 3, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R für eine substituierte aromatische Gruppe steht.

5. Arzneimittel nach Anspruch 4, dadurch gekennzeichnet, daß es sich bei dem Ester der Guanidinobenzoesäure um :
p-(p-Guanidinobenzoyloxy)-phenylessigsäure-N,N-dimethyl-carbamoylmethylester,

p-Guanidinobenzoesäure-p-sulfamoylphenylester oder
p-Guanidinobenzoesäure-6-amidinonaphth-2-ylester
oder ein nicht-toxisches Säureadditionssalz derselben handelt.

6. Arzneimittel nach Anspruch 3, dadurch gekennzeichnet, daß es bei dem Ester der Benzoesäure um p-Guanidino-benzoesäuremethylester oder ein nicht-toxisches Säureadditionssalz desselben handelt.

7. Arzneimittel nach Anspruch 2, dadurch gekennzeichnet, daß es sich bei dem Ester der Benzoesäure um Salicylsäureethylester handelt.

8. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Ester um einen Ester von Thromboxananalogen handelt.

9. Arzneimittel nach Anspruch 8, dadurch gekennzeichnet, daß es sich bei dem Ester von Thromboxananalogen um einen Alkylester der 7-(3-Tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptensäure handelt.

10. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Amid von Prostaglandinanalogen handelt.

11. Arzneimittel nach Anspruch 10, dadurch gekennzeichnet, daß es sich bei dem Amid von Prostaglandinanalogen um ein Amid von 6-Keto-16S,18S-ethano-20-ethyl-PGE_1 mit einer Aminosäure handelt.

12. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Amid der Benzoesäure handelt.

13. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Amid von Thromboxananalogen handelt.

14. Arzneimittel nach Anspruch 13, dadurch gekennzeichnet, daß es sich bei dem Amid von Thromboxananalogen um ein Amid von 7-(3-Tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptensäure mit einer Aminosäure handelt.

15. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Prolinal- oder Thiazolidinderivat mit Amidobindungen handelt.

16. Arzneimittel nach Anspruch 15, dadurch gekennzeichnet, daß es sich bei dem Prolinal- oder Thiazolidinderivat mit Amidobindungen um N-[3-[N-(4-Chlorbenzyl)-carbamoyl]-propanoyl]-L-prolinal handelt.

17. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem mittelkettigen Glycerid um ein Glycerid der Caprylsäure oder ein Glycerid der Caprinsäure handelt.

18. Arzneimittel nach Anspruch 17, dadurch gekennzeichnet, daß es sich bei dem mittelkettigen Glycerid um Glycerylmonocaprylat, Glyceryldicaprylat oder Glyceryltricaprylat oder eine Mischung derselben handelt.

19. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß es in eine Kapsel abgefüllt ist.

20. Arzneimittel nach Anspruch 19, dadurch gekennzeichnet, daß die Kapsel mit einem enterischen Überzug versehen ist.

21. Arzneimittel nach Anspruch 20, dadurch gekennzeichnet, daß der enterische Überzug aus Carboxymethylethylcellulose, Hydroxypropylmethylcelluloseacetatsuccinat oder Phospholipiden besteht.

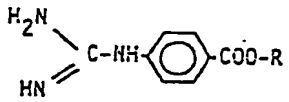
22. Verfahren zur Zubereitung eines Arzneimittels, bei dem eine Verbindung, ausgewählt aus einem Ester der Benzoesäure oder von Thromboxananalogen, einem Amid der Benzoesäure, von Thromboxananalogen oder Prostaglandinanalogen und Prolinal- oder Thiazolidinderivaten mit Amidobindung(en), in einem mittelkettigen Glycerid oder einer Mischung aus zwei oder mehreren derselben suspendiert oder gelöst wird.

Patentansprüche für die Vertraggstaaten : ES, GR.

1. Verfahren zur Zubereitung eines Arzneimittels, bei dem eine Verbindung, ausgewählt aus einem Ester der Benzoesäure oder von Thromboxananalogen, einem Amid der Benzoesäure, von Thromboxananalogen oder Prostaglandinanalogen und Prolinal- oder Thiazolidinderivaten mit Amidobindung(en), in einem mittelkettigen Glycerid oder einer Mischung aus zwei oder mehreren derselben suspendiert oder gelöst wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß der Ester aus einem Ester der Benzoesäure besteht.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß der Ester der Benzoesäure aus einer Verbindung der allgemeinen Formel :



(I)

worin R für eine organische Gruppe steht, oder einem nicht-toxischen Säureadditionssalz derselben besteht.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R für eine substituierte aromatische Gruppe steht.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß es sich bei dem Ester der Guanidinobenzoesäure um:
p-(p-Guanidinobenzoyloxy)-phenylessigsäure-N,N-dimethyl-carbamoylmethylester,
p-Guanidinobenzoesäure-p-sulfamoylphenylester oder
p-Guanidinobenzoesäure-6-amidinonaphth-2-ylester
oder ein nicht-toxisches Säureadditionssalz derselben handelt.

6. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß es bei dem Ester der Benzoesäure um p-Guanidinobenzoesäuremethylester oder ein nicht-toxisches Säureadditionssalz desselben handelt.

7. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß es sich bei dem Ester der Benzoesäure um Salicylsäureethylester handelt.

8. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Ester um einen Ester von Thromboxananalogen handelt.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß es sich bei dem Ester von Thromboxananalogen um einen Alkylester der 7-(3-Tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptensäure handelt.

10. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Amid von Prostaglandinanalogen handelt.

11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß es sich bei dem Amid von Prostaglandinanalogen um ein Amid von 6-Keto-16S,18S-ethano-20-ethyl-PGE_1 mit einer Aminosäure handelt.

12. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Amid der Benzoesäure handelt.

13. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Amid von Thromboxananalogen handelt.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß es sich bei dem Amid von Thromboxananalogen um ein Amid von 7-(3-Tosylaminobicyclo[2.2.1]heptan-2-yl)-5Z-heptensäure mit einer Aminosäure handelt.

15. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Amid um ein Prolinal- oder Thiazolidinderivat mit Amidobindungen handelt.

16. Verfahren nach Anspruch 15, dadurch gekennzeichnet, daß es sich bei dem Prolinal- oder Thiazolidinderivat mit Amidobindungen um N-[3-[N-(4-Chlorbenzyl)-carbamoyl]-propanoyl]-L-prolinal handelt.

17. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem mittelkettigen Glycerid um ein Glycerid der Caprylsäure oder ein Glycerid der Caprinsäure handelt.

18. Verfahren nach Anspruch 17, dadurch gekennzeichnet, daß es sich bei dem mittelkettigen Glycerid um Glycerylmonocaprylat, Glyceryldicaprylat oder Glyceryltricaprylat oder eine Mischung derselben handelt.

19. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß es in eine Kapsel abgefüllt ist.

20. Verfahren nach Anspruch 19, dadurch gekennzeichnet, daß die Kapsel mit einem enterischen Überzug versehen ist.

21. Verfahren nach Anspruch 20, dadurch gekennzeichnet, daß der enterische Überzug aus Carboxymethylethylcellulose, Hydroxypropylmethylcelluloseacetatsuccinat oder Phospholipiden besteht.

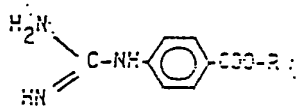
Revendications

Revendications pour les Etats contractants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. Composition pharmaceutique constituée essentiellement d'un composé choisi parmi un ester de l'acide benzoïque ou d'analogues du thromboxane, un amide de l'acide benzoïque, d'analogues du thromboxane ou d'analogues de prostaglandine, et des dérivés du prolinal ou de la thiazolidine ayant une ou plusieurs liaisons amido, en suspension ou en solution dans un glycéride à chaîne moyenne ou un mélange de deux ou plusieurs d'entre eux.

2. Composition pharmaceutique selon la revendication 1, dans laquelle ledit ester est un ester d'acide benzoïque.

3. Composition pharmaceutique selon la revendication 2, dans laquelle ledit ester d'acide benzoïque est un composé de formule générale :



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(dans laquelle R est un groupe organique) ou un sel d'addition d'acide non toxique de celui-ci.

4. Composition pharmaceutique selon la revendication 3, dans laquelle R est un groupe aromatique substitué dans la formule générale (I).

5. Composition pharmaceutique selon la revendication 4, dans laquelle l'ester d'acide guanidinobenzoïque est l'ester N,N-diméthyl-carbamoylméthylique de l'acide p-(p-guanidinobenzoyloxy)phényl-acétique, l'ester p-sulfamoylphénylique de l'acide p-guanidinobenzoïque, l'ester 6-amidino-napht-2-ylique de l'acide p-guanidinobenzoïque ou un sel d'addition d'acide non toxique de ceux-ci.

6. Composition pharmaceutique selon la revendication 3, dans laquelle ledit ester d'acide benzoïque est l'ester méthylique de l'acide p-guanidinobenzoïque ou un sel d'addition d'acide non toxique de celui-ci.

7. Composition pharmaceutique selon la revendication 2, dans laquelle ledit ester d'acide benzoïque est l'ester éthylique de l'acide salicylique.

8. Composition pharmaceutique selon la revendication 1, dans laquelle ledit ester est un ester d'analogues du thromboxane.

9. Composition pharmaceutique selon la revendication 8, dans laquelle ledit ester d'analogues du thromboxane est un ester alkylique de l'acide 7-(3-tosylaminobicyclo[2.2.1]heptane-2-yl)-5Z-hepténoïque.

10. Composition pharmaceutique selon la revendication 1, dans laquelle ledit amide est un amide d'analogues de prostaglandine.

11. Composition pharmaceutique selon la revendication 10, dans laquelle ledit amide d'analogues de prostaglandine est un amide de la 6-céto-16S,18S-éthano-20-éthyl-PGE$_1$ et d'un amino-acide.

12. Composition pharmaceutique selon la revendication 1, dans laquelle ledit amide est un amide d'acide benzoïque.

13. Composition pharmaceutique selon la revendication 1, dans laquelle ledit amide est un amide d'analogues du thromboxane.

14. Composition pharmaceutique selon la revendication 13, dans laquelle ledit amide d'analogues du thromboxane est un amide d'acide 7-(3-tosylaminobicyclo[2.2.1]heptane-2-yl)-5Z-hepténoïque et d'un amino-acide.

15. Composition pharmaceutique selon la revendication 1, dans laquelle ledit amide est un dérivé de prolinal ou de thiazolidine ayant des liaisons amido.

16. Composition pharmaceutique selon la revendication 15, dans laquelle ledit dérivé du prolinal ou de la thiazolidine ayant des liaisons amido est le N-[3-[N-(4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal.

17. Composition pharmaceutique selon la revendication 1, dans laquelle ledit glycéride à chaîne moyenne est un glycéride d'acide caprylique ou un glycéride d'acide caprique.

18. Composition pharmaceutique selon la revendication 17, dans laquelle ledit glycéride à chaîne moyenne est le monocaprylate de glycéryle, le dicaprylate de glycéryle ou le tricaprylate de glycéryle ou un de leurs mélanges.

19. Composition pharmaceutique selon la revendication 1, qui est contenue dans une capsule.

20. Composition pharmaceutique selon la revendication 19, caractérisée en ce que la capsule porte un revêtement à délitage entérique.

21. Composition pharmaceutique selon la revendication 20, caractérisée en ce que le revêtement à délitage entérique est fait de carboxyméthyléthylcellulose, d'acétosuccinate d'hydroxypropylméthylcellulose ou de phospholipides.

22. Procédé pour la préparation d'une composition pharmaceutique, dans lequel un composé choisi parmi un ester d'acide benzoïque ou d'analogues du thromboxane, un amide d'acide benzoïque, d'analogues du thromboxane ou d'analogues de prostaglandine, et les dérivés du prolinal ou de la thiazolidine, ayant une ou plusieurs liaisons amido, est mis en suspension ou dissous dans un glycéride à chaîne moyenne ou un mélange de deux ou plusieurs d'entre eux.

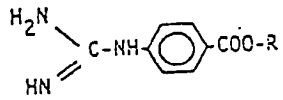
Revendications pour les Etats contractants : ES, GR.

1. Procédé pour la préparation d'une composition pharmaceutique, dans lequel un composé choisi parmi un ester d'acide benzoïque ou d'analogues du thromboxane, un amide d'acide benzoïque, d'analogues du thromboxane ou d'analogues de prostaglandine, et les dérivés du prolinal ou de la thiazolidine, ayant une ou

plusieurs liaisons amido, est mis en suspension ou dissous dans un glycéride à chaîne moyenne ou un mélange de deux ou plusieurs d'entre eux.

2. Procédé selon la revendication 1, dans lequel ledit ester est un ester d'acide benzoïque.

3. Procédé selon la revendication 2, dans lequel ledit ester d'acide benzoïque est un composé de formule générale :



(I)

(dans laquelle R est un groupe organique) ou un sel d'addition d'acide non toxique de celui-ci.

4. Procédé selon la revendication 3, dans lequel R est un groupe aromatique substitué dans la formule générale (I).

5. Procédé selon la revendication 4, dans lequel ledit ester d'acide guanidinobenzoïque est l'ester N,N-diméthylcarbamoylméthylique de l'acide p-(p-guanidinobenzoyloxy)phénylacétique, l'ester p-sulfamoylphénylique de l'acide p-guanidinobenzoïque, l'ester 6-amidino-napht-2-ylique de l'acide p-guanidinobenzoïque ou un sel d'addition d'acide non toxique de ceux-ci.

6. Procédé selon la revendication 3, dans lequel ledit ester d'acide benzoïque est l'ester méthylique de l'acide p-guanidinobenzoïque ou un sel d'addition d'acide non toxique de celui-ci.

7. Procédé selon la revendication 2, dans lequel ledit ester d'acide benzoïque est l'ester éthylique de l'acide salicylique.

8. Procédé selon la revendication 1, dans lequel ledit ester est un ester d'analogues du thromboxane.

9. Procédé selon la revendication 8, dans lequel ledit ester d'analogues du thromboxane est un ester alkylique de l'acide 7-(3-tosylaminobicyclo[2.2.1]heptane-2-yl)-5Z-hepténoïque.

10. Procédé selon la revendication 1, dans lequel ledit amide est un amide d'analogues de prostaglandine.

11. Procédé selon la revendication 10, dans lequel ledit amide d'analogues de prostaglandine est un amide de la 6-céto-16S,18S-éthano-20-éthyl-PGE$_1$ et d'un amino-acide.

12. Procédé selon la revendication 1, dans lequel ledit amide est un amide d'acide benzoïque.

13. Procédé selon la revendication 1, dans lequel ledit amide est un amide d'analogues du thromboxane.

14. Procédé selon la revendication 13, dans lequel ledit amide d'analogues du thromboxane est un amide d'acide 7-(3-tosylamino-bicyclo[2.2.1]heptane-2-yl)-5Z-hepténoïque et d'un amino-acide.

15. Procédé selon la revendication 1, dans lequel ledit amide est un dérivé de prolinal ou de thiazolidine ayant des liaisons amido.

16. Procédé selon la revendication 15, dans lequel ledit dérivé du prolinal ou de la thiazolidine ayant des liaisons amido est le N-[3-[N-(4-chlorobenzyl)carbamoyl]propanoyl]-L-prolinal.

17. Procédé selon la revendication 1, dans lequel ledit glycéride à chaîne moyenne est un glycéride d'acide caprylique ou un glycéride d'acide caprique.

18. Procédé selon la revendication 17, dans lequel ledit glycéride à chaîne moyenne est le monocaprylate de glycéryle, le dicaprylate de glycéryle ou le tricaprylate de glycéryle ou un de leurs mélanges.

19. Procédé selon la revendication 1, dans lequel ladite composition pharmaceutique est contenue dans une capsule.

20. Procédé selon la revendication 19, caractérisé en ce que la capsule porte un revêtement à délitage entérique.

21. Procédé selon la revendication 20, caractérisé en ce que le revêtement à délitage entérique est fait de carboxyméthyléthylcellulose, d'acétosuccinate d'hydroxypropylméthylcellulose ou de phospholipides.

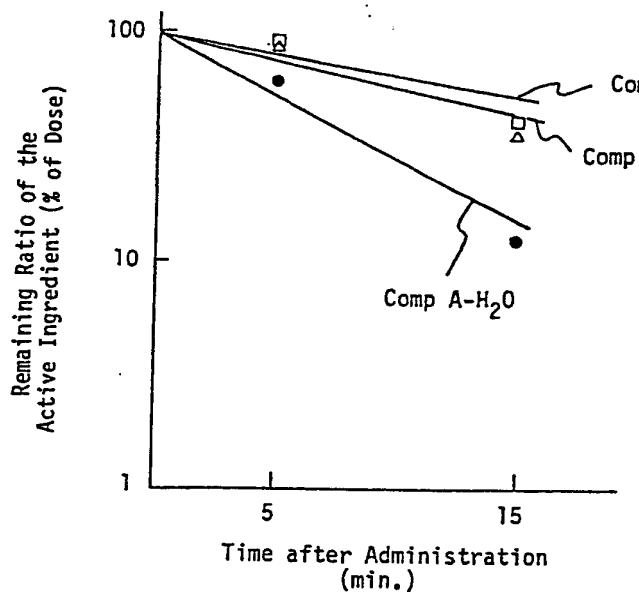


Figure 1

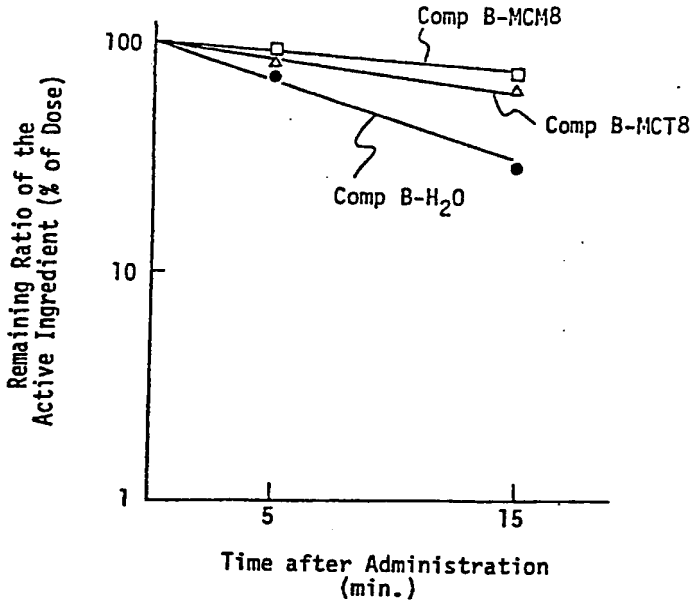


Figure 2

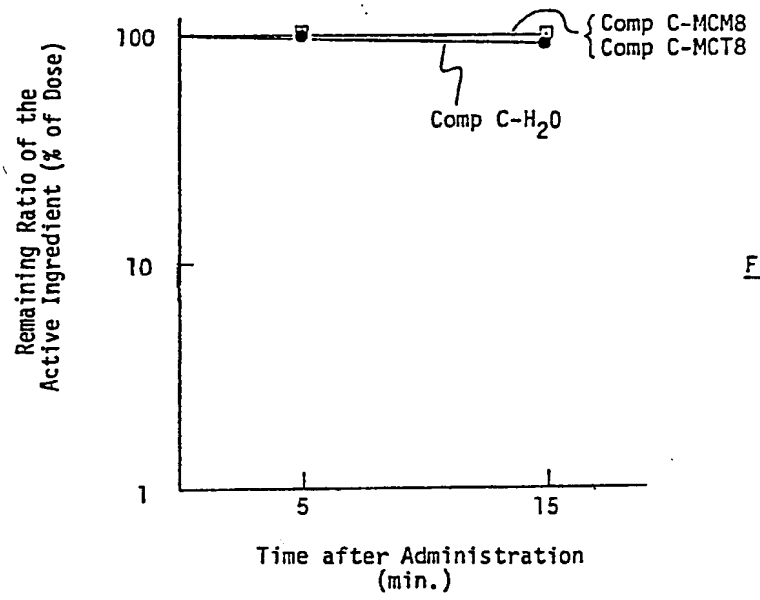


Figure 3

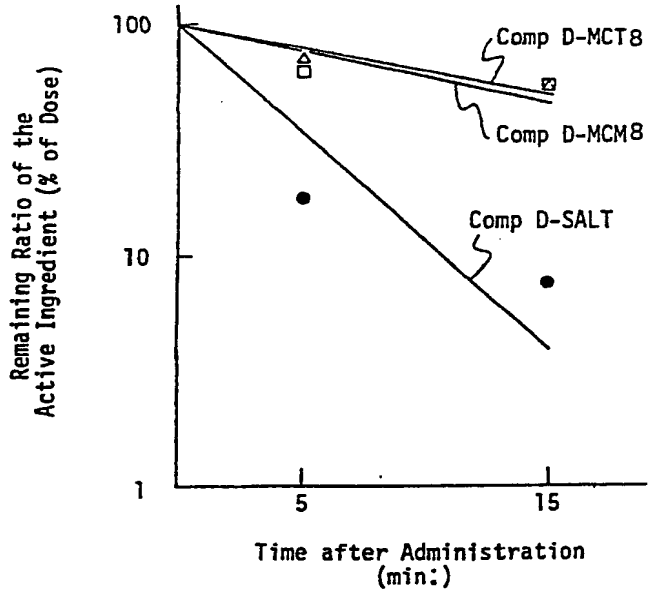


Figure 4

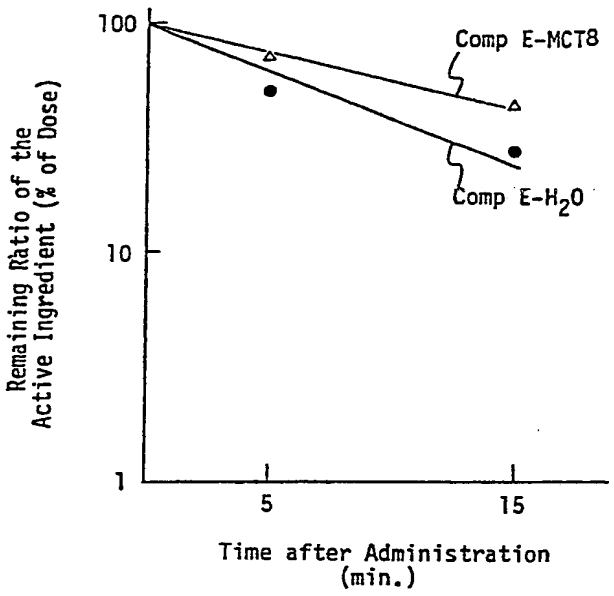

100
10
1
Remaining Ratio of the Active Ingredient (% of Dose)
Comp E-MCT8
Comp E-H2O
5
15
Time after Administration (min.)

Figure 5

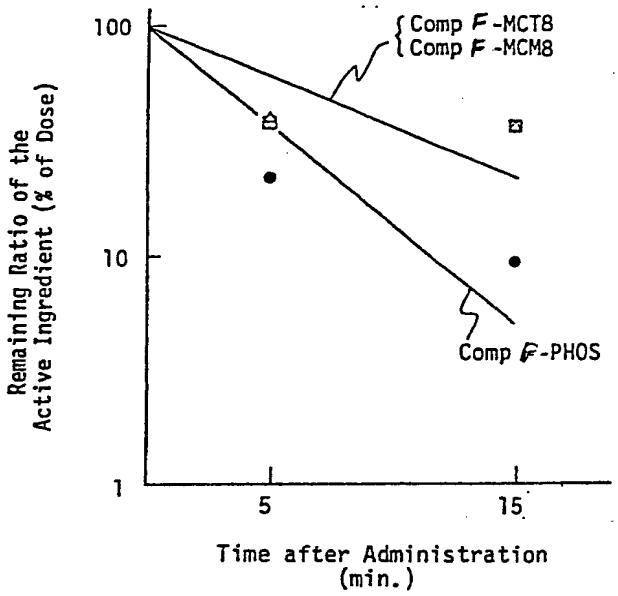


Figure 6

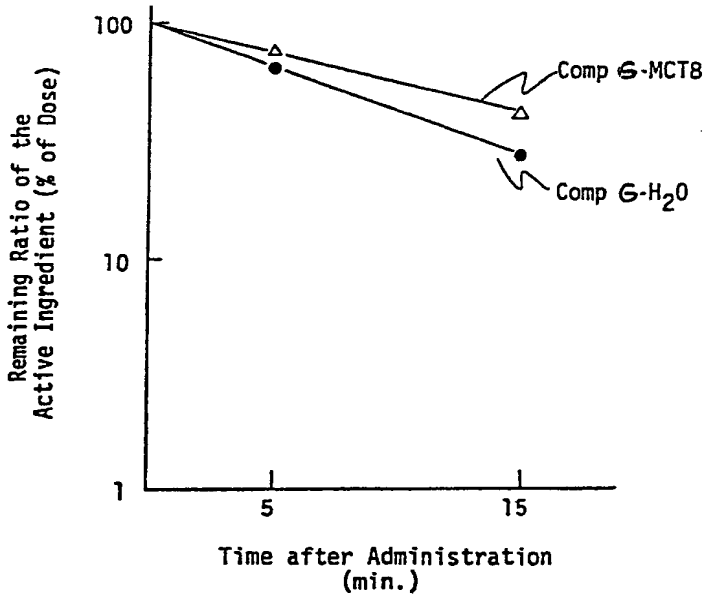


Figure 7

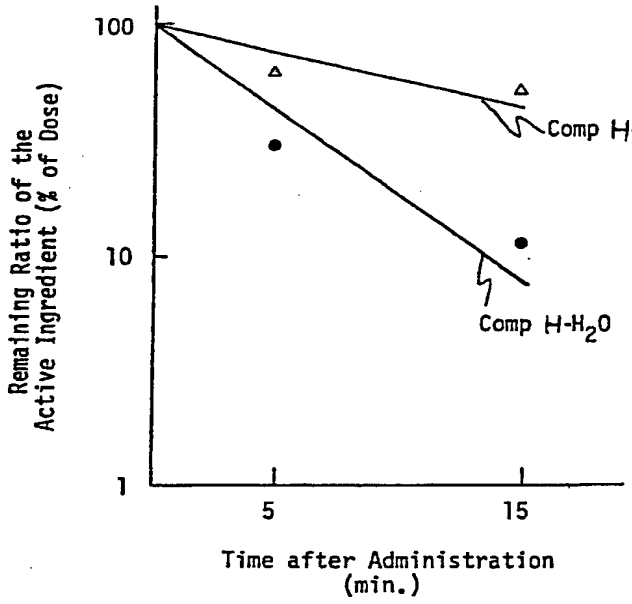

100
10
1
Remaining Ratio of the Active Ingredient (% of Dose)
Comp H-MCT8
Comp H-H2O
5
15
Time after Administration (min.)

Figure 8